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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/582,916	10/02/2000	Carl Anthony Blau	UOFW115624	4343

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ART UNIT	PAPER NUMBER
1632	17

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/582,916	BLAU ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-88* is/are pending in the application.

4a) Of the above claim(s) *43,54,67-69 and 77-88* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-42,44-53,55-66 and 70-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment and response received 5/23/03 has been entered. Claims 1-88 are pending in the instant application. This application contains claims 43, 54, 67-69, and 77-88 drawn to an invention nonelected without traverse in Paper No. 12. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01. Claims 1-42, 44-53, 55-66, and 70-76 are currently under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in a previous office action.

Claim Rejections - 35 USC § 102

The rejection of claims 1-42, 44-53, 55-66, and 70-76 under 35 U.S.C. 102(e) as being anticipated over U.S. Patent No. 5,741,899 (4/21/98), hereafter referred to as Capon et al., is maintained. Applicant's arguments have been fully considered but have not been found to be persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that Capon et al. does not provide an enabling disclosure for drug-induced proliferation of primary cells using CPRs, transduction of cells in a mammal with DNA encoding a CPR, or administering a drug to a mammal. Specifically, the applicant argues that the only description of CPRs in primary cells provided by Capon et al. is Example 11, and that this example is prophetic and does not actually show that the transfected cells proliferate or differentiate in response to an inducer. The applicant further argues that although Example 11 mentions FK1012, it would be ineffective to stimulate the CPRs of Example 11 because these CPRs do not comprise FKBP. In response, the disclosure of Capon et al. relating to a fusion protein comprising at least one signaling domain and at least one heterologous drug-binding domain is not limited to Example 11. As noted in the previous office action, Capon et al. teaches that the extracellular or intracellular inducer-responsive clustering domain of the chimeric protein is derived from immunophilin, e.g. FKBP, and that the cytoplasmic signal transduction domain is derived from homodimerizing receptors such as G-CSFR, EPO-R, GHR, PRLR, TPOR, and gp130 (Capon et al., column 7, lines 8-15, column 9, lines 4-21, column 13, lines 35-38, column 15, lines 1-16, columns 34-35, example 7, and columns 42-43). In particular, example 7, columns 34-35 provides detailed direction for making vectors encoding an FKBP fusion protein. Examples 8-9 also provided detailed directions for making FKBP fusion proteins. Capon et al. further teaches that cells transduced with an appropriate vector, such as a viral vector or DNA plasmid, encoding said chimeric protein can be induced to expand and proliferate by exposing the cells to a multivalent inducer molecule capable of binding to the inducer binding domain of the fusion

protein. In the case of chimeric proteins which encode FKBP, Capon et al. teaches that the inducer molecule is a multivalent cell-permeant drug with a molecule weight of less than 5 kD such as FK1012 (Capon et al., columns 15, 19, 21 and 22). In addition, section g) of example 11 is clearly not limited to a description of inducing proliferation using the fusion proteins particularly disclosed in section a) of example 11. The end of section a) states that the description provided for making retroviral vectors encoding CPRs can readily be used by the skilled artisan to make other retroviral vectors encoding other CPRs disclosed in the Capon specification. The fact that section g) teaches using FK1012 as the inducer of proliferation clearly refers to FKBP fusion proteins disclosed in examples 7-9.

As noted by the applicant, an anticipating reference "must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter". Clearly from the detailed directions present in Example 7-9 for making FKBP fusion proteins and the clear teachings regarding the use of different cytoplasmic signaling domains with FKBP, the skilled artisan would have been able to genetically engineer primary cells to contain recombinant DNA encoding a fusion protein consisting of a drug binding domain and a signaling domain by following the teachings of the Capon specification. Please note as well that claims 44-53, and 55 are product claims drawn to the recombinant cells themselves and not to methods of using the cells.

Regarding the method claims, claims 1-18, 55, 58-62, and 65 are drawn to methods of using cells transduced *ex vivo*. Claims 19-20 are drawn to methods of transducing the cells *in*

vivo. These claims, while reciting that exposure of these cells to a selected drug results in growth, proliferation, or differentiation of the cells, do not actually include the step of administering the drug to the mammal or exposing the cells to the drug *ex vivo*. Capon et al. teaches that target cells for expansion can be transduced *in vitro* or *in vivo* for use in the treatment of human diseases such as cancer or autoimmune disease (Capon et al., columns 1, 16, 19, and 21-22). In regards to cells transduced *ex vivo* and introduced into the host mammal, Capon et al. teaches that the cells can be allogeneic or autologous cells, including hematopoietic stem cells capable of developing into cells of the myeloid and lymphoid lineages (Capon et al., columns 16, and 21-22). While the applicant seems to argue that Capon et al. does not teach the direct administration of the vectors encoding CPRs to a host mammal, Capon et al. in column 19, lines 18-27, clearly teaches that host cells can be transformed using biolistics which utilize DNA-coated particles, or by direct injection of naked DNA. At the time of filing, DNA biolistics, more commonly referred to as the gene gun method, was well known as a method of introducing DNA into cells *in vivo*. The state of the art of DNA biolistics at the time of filing does not teach using gene gun technology for transducing cells in tissue culture. The gene gun device is specifically designed to shoot DNA-coated particles, usually gold beads, into living tissue using high pressure. Further, direct injection of naked DNA is also an art recognized and commonly known technique for introducing plasmid DNA into cells *in vivo* in the absence of transfection facilitating agents. Direct injection of cells in tissue culture is referred to as microinjection, not as direct injection of naked DNA. Thus, the skilled artisan at the time of filing would clearly understand by reading the Capon

specification that direct injection of the disclosed DNAs encoding CPRs *in vivo* was contemplated and enabled.

Furthermore, in regards to the particular use of the method taught by Capon et al. to treat hematopoietic disease or pathological conditions in a mammal or to obtain megakaryocytes, neutrophils, or erythrocytes in vivo or in vitro, the previous office action noted that the methods for inducing the proliferation of hematopoietic stem cells taught by Capon et al. include the exact same method steps as those recited in claims 56-66 and 70-76. It is a general rule that merely discovering and claiming a new benefit to an old process cannot render the process again patentable. In re Woodruff, 919 F. 2d 1575, 1577-78, 16 USPQ2d 1934, 1936-37 (Fed.Cir. 1990); In re Swinehart, 439 F.2d 210, 213, 169 USPQ 226, 229 (CCPA 1971); and Ex Parte Novitski, 26 USPQ2d 1389, 1391 (Bd. Pat. App. & Int. 1993). In addition, Capon et al. does specifically teach the use of the disclosed methods for treating disease, and clearly teaches that hematopoietic stem cells develop into myeloid and lymphoid cells (Capon et al., columns 16 and 21-22). The MPEP also states that "when the claim recites using an old composition or structure and the 'use' is directed to a result or property of that composition or structure, then the claim is anticipated. *In re May*, 574 F. 2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978)" MPEP 2112.02. Thus, by teaching the exact same compositions and method steps recited in the instant claims, Capon et al. anticipates the instant invention as claimed.

Regarding the administration of the drug to cells *in vitro* or *in vivo* to induce proliferation, growth, or differentiation of cells expressing the fusion protein, see applicant's method claims 21-

42, 57, 63-64, 66, and 70-76, the Capon specification clearly teaches that cellular proliferation can be induced by exposing the cells expressing the CPR to an inducer. In the abstract, Capon states that binding of inducer to the CPR induces clustering of the binding domains to each other and further signals the cell to proliferate. In column 1, Capon states that the disclosed invention provides methods for directing cell proliferation *in vivo* by inducing cells expressing CPRs to proliferate in response to an administered inducer molecule (Capon, column 1, lines 45-55). In column 6, lines 47-54), Capon et al. teaches that cells constructed to express CPRs proliferate in response to an inducer molecule, and particularly gives the example of FKBP-JAK1 as the CPR. Column 7, lines 11-15, continues by teaching that inducer molecules capable of inducing proliferation are ligands that bind and induce clustering of FKBP. In column 15, lines 10-16, Capon et al. further specifically teaches that the drug, FK1012, a non-protein drug which has a molecular weight less than 5kD and which is cell-permeant, can be used as an inducer to cluster the FKBP domains in a CPR. Finally, Capon et al. in column 21, lines 1-15, teaches, " Chimeric proliferation receptors which do not contain effector function signaling domains may also be of use in the treatment of human disease. Various cell types containing the CPR constructs described above may be grown in an appropriate nutrient medium for expansion or **may be expanded directly in the body via signaling through the CPR**.." (emphasis added). Thus, throughout the specification, Capon et al. teaches expanding cells by exposing them to an inducer molecule, and further teaches that the exposure to the inducer molecule can occur *ex vivo* or *in vivo*.

Finally, regarding applicant's statements that Blau et al. and Sikorski et al., both published in 1997, teach that the results provided in Blau et al. represent the first example of cell proliferation dependent on a synthetic drug, it is noted that the Capon et al. patent was not published until 1998, and therefore the teachings of Capon et al. were not available to the public in 1997. Capon et al. qualifies as prior art over the instant invention under 102(e) based on the filing date of the Capon patent.

Therefore, despite applicant's arguments to the contrary, the office finds that a fair reading of Capon et al. demonstrates that Capon et al. not only teaches all the elements of the claims as written, but further provides an enabling disclosure for making and using the vectors and cells disclosed therein. As such, Capon et al. anticipates the instant invention as claimed, and the rejection of record stands.

No claims are allowed.

Information Disclosure Statement

The supplemental information disclosure statement filed 5/23/03, paper no. 15, has been entered and considered by the examiner of record. A signed copy of the 1449 is attached to the instant office action.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Fri from 10:30-7:00 EST. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER